

*Variant: NM\_025114.4(CEP290):c.963T>A (p.Asp321Glu)*

Version: 1.0

CA6712647 [↗](#)

286797 (ClinVar) [↗](#)

**Gene:** CEP290 ([HGNC:80184](#))

**Condition:** CEP290-related ciliopathy ([MONDO:0100451](#))

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 76c0995b-fdf7-4888-9473-ef9e2125d571

**Approved on:** 2026/7/20

**Published on:** 2026/7/20

### *HGVS expressions*

**NM\_025114.4(CEP290):c.963T>A (p.Asp321Glu)**

**NM\_025114.4:c.963T>A**

NC\_000012.12:g.88126418A>T

CM000674.2:g.88126418A>T

NC\_000012.11:g.88520195A>T

CM000674.1:g.88520195A>T

NC\_000012.10:g.87044326A>T

NG\_008417.1:g.20799T>A

NG\_008417.2:g.20799T>A

ENST00000309041.12:c.963T>A

ENST00000397838.8:c.909T>A

ENST00000547926.7:c.963T>A

ENST00000552810.6:c.963T>A

ENST00000671822.2:n.1190T>A

ENST00000672414.2:c.963T>A

ENST00000673058.2:c.963T>A

ENST00000674971.1:c.963T>A

ENST00000675230.1:c.942T>A

ENST00000675408.1:c.963T>A

ENST00000675476.1:c.963T>A

ENST00000675559.1:c.963T>A

ENST00000675628.1:n.1190T>A

ENST00000675794.1:c.963T>A

ENST00000675833.1:c.963T>A

ENST00000676074.1:c.963T>A

ENST00000676351.1:c.\*476T>A

ENST00000676363.1:n.3026T>A

ENST00000676418.1:c.963T>A

ENST00000676448.1:c.963T>A

ENST00000309041.11:c.963T>A

ENST00000397838.7:c.963T>A

ENST00000547926.6:c.861T>A

ENST00000552810.5:c.963T>A

ENST00000604024.5:c.129T>A

NM\_025114.3:c.963T>A

Uncertain Significance

Met criteria codes 1

PM2\_Supporting

Not Met criteria codes 2

BP4 PM3

Evidence Links 0

Expert Panel

Leber Congenital Amaurosis/early onset Retinal Dystrophy VCEP

Criteria Specification Information

Criteria Specification: ClinGen Leber Congenital Amaurosis/early onset Retinal Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CEP290 Version 1.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Leber Congenital Amaurosis/early onset Retinal Dystrophy VCEP

NM\_025114.4(CEP290):c.963T>A (p.Asp321Glu) is a missense variant that replaces aspartic acid with glutamic acid at amino acid 321. This variant is present in gnomAD v4.1.1 at a total allele frequency of 0.00005764, with 87 alleles / 1,509,276 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2\_Supporting threshold of <0.0006 (PM2\_Supporting). This variant has been reported in at least 1 proband with renal anomalies and renal disease who harbored the variant in the compound heterozygous state, however, the proband was not counted for PM3 because sufficient phenotype details were not reported and because the NM\_025114.4(CEP290):c.5998A>G (p.Ile2000Val) variant suspected in trans has been classified as likely benign (PMID: 40718208). The variant has been reported in a second unpublished proband with retinal disease in the compound heterozygous state, however, the proband was not counted for PM3 because the NM\_025114.4(CEP290):c.1092T>G (p.Ile364Met) variant confirmed in trans has been classified as likely benign (VCEP member-provided data). The computational predictor CADD gives a score of 24.9, which is above the ClinGen LCA/eoRD VCEP BP4 threshold of <17.3 and below the PP3 threshold of ≥25.3, so neither PP3 nor BP4 is met. The splicing impact predictor SpliceAI gives a delta score of 0.03 for acceptor loss, which is below the threshold of <0.1 and does not predict an impact on splicing. In summary, this variant meets the criteria to be classified as a Variant of Uncertain Significance for CEP290-related ciliopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen LCA/eoRD VCEP: PM2\_Supporting. (LCA/eoRD VCEP Specifications for CEP290 Version 1.0.0)

Met criteria codes

PM2\_Supporting

i

✓

This variant is present in gnomAD v4.1.0 at a total allele frequency of 0.00005764, with 87 alleles / 1,509,276 total alleles, which is lower than the ClinGen LCA/eoRD VCEP PM2\_Supporting threshold of <0.0006 (PM2\_Supporting).

Not Met criteria codes

BP4

i

✗

The computational predictor CADD gives a score of 24.9, which is above the ClinGen LCA/eoRD VCEP threshold of <17.3 and does not predict a non-damaging effect on CEP290. The splicing impact predictor SpliceAI gives a delta score of 0.03 for acceptor loss, which is below the threshold of <0.1 and does not predict an impact on splicing.

PM3

i

✗

This variant has been reported in at least 1 proband with renal anomalies and renal disease who harbored the variant in the compound heterozygous state, however, the proband was not counted for PM3 because sufficient phenotype details were not reported and because the NM\_025114.4(CEP290):c.5998A>G (p.Ile2000Val) variant suspected in trans has been classified as likely benign (PMID: 40718208). The variant has been reported in a second unpublished proband with retinal disease in the compound heterozygous state, however, the proband was not

counted for PM3 because the NM\_025114.4(CEP290):c.1092T>G (p.Ile364Met) variant confirmed in trans has been classified as likely benign (VCEP member-provided data).

Curation History [↗](#)

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